Claims

What is claimed is:

1. A cyclic peptide comprising the sequence His-Ala-Val, wherein said cyclic peptide modulates cadherin-mediated cell adhesion.

2. A cyclic peptide according to claim 1, having the formula:

(Z_1)-(Y_1)-(X_1)-His-Ala-Val-(X_2)-(Y_2)-(Z_2)

wherein X_1, and X_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds, and wherein X_1 and X_2 independently range in size from 0 to 10 residues, such that the sum of residues contained within X_1 and X_2 ranges from 1 to 12;

wherein Y_1 and Y_2 are independently selected from the group consisting of amino acid residues, and wherein a covalent bond is formed between residues Y_1 and Y_2; and

wherein Z_1 and Z_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds.

3. A cyclic peptide according to claim 2, wherein Z_1 is not present and Y_1 comprises an N-acetyl group.

4. A cyclic peptide according to claim 2, wherein Z_2 is not present and Y_2 comprises a C-terminal amide group.

5. A cyclic peptide according to claim 2, wherein Y_1 and Y_2 are covalently linked via a disulfide bond.

6. A cyclic peptide according to claim 5, wherein Y_1 and Y_2 are each independently selected from the group consisting of penicillamine, β,β-tetramethylene cysteine, β,β-pentamethylene cysteine, β-mercaptopropionic acid, β,β-pentamethylene-β-mercaptopropionic acid, 2-mercaptobenzene, 2-mercaptoaniline, 2-mercaptoproline and derivatives thereof.

7. A cyclic peptide according to claim 5, wherein Y_1 and Y_2 are cysteine residues or derivatives thereof.

8. A cyclic peptide according to claim 7, wherein said cyclic peptide comprises the sequence Cys-His-Ala-Val-Cys (SEQ ID NO:8).

9. A cyclic peptide according to claim 8, further comprising an N-acetyl group.

10. A cyclic peptide according to claim 8, further comprising a C-terminal amide group.

11. A cyclic peptide according to claim 7, wherein said cyclic peptide comprises a sequence selected from the group consisting of Cys-Ala-His-Ala-Val-Asp-Ile-Cys (SEQ ID NO:10), Cys-Ser-His-Ala-Val-Cys (SEQ ID NO:12), Cys-His-Ala-Val-Ser-Cys (SEQ ID NO:14), Cys-Ala-His-Ala-Val-Asp-Cys (SEQ ID NO:16) and Cys-Ser-His-Ala-Val-Ser-Ser-Cys (SEQ ID NO:18).

12. A cyclic peptide according to claim 2, wherein Y_1 and Y_2 are covalently linked via an amide bond.

13. A cyclic peptide according to claim 12, wherein said amide bond is formed is formed between terminal functional groups.

14. A cyclic peptide according to claim 12, wherein said amide bond is formed between residue side-chains.

15. A cyclic peptide according to claim 12, wherein said amide bond is formed between one terminal functional group and one residue side chain.

16. A cyclic peptide according to claim 12, wherein:

(a) Y_1 is selected from the group consisting of lysine, ornithine, and derivatives thereof and Y_2 is selected from the group consisting of aspartate, glutamate and derivatives thereof; or

(b) Y_2 is selected from the group consisting of lysine, ornithine and derivatives thereof and Y_1 is selected from the group consisting of aspartate, glutamate and derivatives thereof.

17. A cyclic peptide according to claim 12, wherein said cyclic peptide comprises the sequence Lys-His-Ala-Val-Asp (SEQ ID NO:20) or Ala-His-Ala-Val-Asp-Ile (SEQ ID NO:44).

18. A cyclic peptide according to claim 2, wherein Y_1 and Y_2 are covalently linked via a thioether bond.

19. A cyclic peptide according to claim 2, wherein Y_1 and Y_2 are each tryptophan or a derivative thereof, such that said covalent bond generates a $\delta_1\delta_1$-ditryptophan, or a derivative thereof.

20. A cyclic peptide according to any one of claims 1-19 linked to a targeting agent.

21. A cyclic peptide according to any one of claims 1-19 linked to a drug.

22. A cyclic peptide according to any one of claims 1-19 linked to a solid support.

23. A cyclic peptide according to claim 22, wherein said solid support is a polymeric matrix.

24. A cyclic peptide according to claim 23, wherein said solid support is selected from the group consisting of plastic dishes, plastic tubes, sutures, membranes, ultra thin films, bioreactors and microparticles.

25. A cyclic peptide according to any one of claims 1-19 linked to a molecule comprising a binding site for an adhesion molecule, wherein said adhesion molecule is not a cadherin.

26. A cyclic peptide according to any one of claims 1-19 linked to a detectable marker.

27. A pharmaceutical composition comprising a cyclic peptide according to any one of claims 1-19 in combination with a pharmaceutically acceptable carrier.

28. A composition according to claim 27, further comprising a drug.

29. A composition according to claim 28, wherein said drug is linked to said cyclic peptide.

30. A composition according to claim 27, wherein said cyclic peptide is present within a sustained-release formulation.

31. A method for modulating cell adhesion, comprising contacting a cadherin-expressing cell with a cyclic peptide according to any one of claims 1-19.

32. A method according to claim 31, wherein said cadherin is selected from the group consisting of E-cadherin and N-cadherin.

33. A method according to claim 31, wherein said cadherin is selected from the group consisting of P-cadherin, R-cadherin and other cadherins comprising the call adhesion recognition sequence HAV.

34. A method according to claim 31, wherein said cell is selected from the group consisting of epithelial cells, endothelial cells, neural cells, tumor cells and lymphocytes.

35. A method according to claim 31, wherein said cyclic peptide inhibits cell adhesion.

36. A method for reducing unwanted cellular adhesions in a mammal, comprising administering to a mammal a cyclic peptide according to any one of claims 1-19.

37. A method for enhancing the delivery of a drug through the skin of a mammal, comprising contacting epithelial cells of a mammal with a cyclic peptide according to any one of claims 1-19 and a drug under conditions and for a time sufficient to allow passage of said drug across said epithelial cells.

38. A method according to claim 37, wherein said cyclic peptide passes into the blood stream of said mammal.

39. A method for enhancing the delivery of a drug to a tumor in a mammal, comprising administering to a mammal a composition according to claim 28.

40. A method according to claim 39, wherein said composition is administered to said tumor.

41. A method according to claim 39, wherein the tumor is selected from the group consisting of bladder tumors, ovarian tumors and melanomas.

42. A method according to claim 39, wherein said composition is administered by injection.

43. A method according to claim 39, wherein said composition is administered topically.

44. A method according to claim 39, wherein said composition is administered systemically.

45. A method for treating cancer in a mammal, comprising administering to a mammal afflicted with cancer a composition according to claim 27.

46. A method according to claim 45, wherein said cancer is selected from the group consisting of carcinomas, leukemia and melanomas.

47. A method for inhibiting metastasis of tumor cells in a mammal, comprising administering to a mammal a composition according to claim 26.

48. A method for inhibiting angiogenesis in a mammal, comprising administering to a mammal a composition according to claim 27.

49. A method for enhancing drug delivery to the brain of a mammal, comprising administering to a mammal a composition according to claim 28.

50. A method according to claim 49, wherein said composition is administered by injection.

51. A method according to claim 31, wherein said cyclic peptide enhances cell adhesion.

52. A method for enhancing wound healing in a mammal, comprising contacting a wound in a mammal with a cyclic peptide according to claim 23.

53. A method according to claim 52, wherein said composition comprises a cyclic peptide according to claim 3.

54. A method for enhancing adhesion of foreign tissue implanted within a mammal, comprising contacting a site of implantation of foreign tissue in a mammal with a cyclic peptide according to claim 23.

55. A method according to claim 54, wherein said foreign tissue is a skin graft or organ implant.

56. A method for inducing apoptosis in a cadherin-expressing cell, comprising contacting a cadherin-expressing cell with a cyclic peptide according to any one of claims 1-19.

57. A method for enhancing and/or directing neurite outgrowth, comprising contacting a neuron with a cyclic peptide according to any one of claims 1-19.

58. A method for treating spinal cord injuries in a mammal, comprising administering to a mammal a composition according to claim 27.

59. A method for treating spinal cord injuries in a mammal, comprising administering to a mammal a cyclic peptide according to claim 23.

60. A method for treating a demyelinating neurological disease in a mammal, comprising administering to a mammal a composition according to claim 28.

61. A method according to claim 60, wherein said disease is multiple sclerosis.

62. A method for modulating the immune system of a mammal, comprising administering to a mammal a composition according to claim 27.

63. A method for preventing pregnancy in a mammal, comprising administering to a mammal a composition according to claim 30.

64. A method according to claim 63, wherein the step of administering is intravaginal or intrauterine.

65. A method for increasing vasopermeability in a mammal, comprising administering to a mammal a composition according to claim 27.

66. A method for identifying a cyclic peptide capable of modulating cadherin-mediated cell adhesion, comprising:

(a) culturing neurons on a monolayer of cells that express N-cadherin in the presence and absence of a candidate cyclic peptide, under conditions and for a time sufficient to allow neurite outgrowth;

(b) determining a mean neurite length for said neurons; and

(c) comparing the mean neurite length for neurons cultured in the presence of candidate cyclic peptide to the neurite length for neurons cultured in the absence of candidate cyclic peptide, and therefrom identifying a cyclic peptide capable of modulating cell adhesion.

67. A method for identifying a cyclic peptide capable of modulating cadherin-mediated cell adhesion, comprising:

(a) culturing cells that express a cadherin in the presence and absence of a candidate cyclic peptide, under conditions and for a time sufficient to allow cell adhesion; and

(b) visually evaluating the extent of cell adhesion among said cells, and therefrom identifying a cyclic peptide capable of modulating cell adhesion.

68. A method according to claim 67, wherein said cells are selected from the group consisting of endothelial, epithelial and cancer cells.

69. A method for identifying a cyclic peptide capable of modulating cadherin-mediated cell adhesion, comprising:

(a) culturing NRK cells in the presence and absence of a candidate cyclic peptide, under conditions and for a time sufficient to allow cell adhesion;

(b) comparing the level of cell surface E-cadherin for cells cultured in the presence of candidate cyclic peptide to the level for cells cultured in the absence of candidate cyclic peptide, and therefrom identifying a cyclic peptide capable of modulating cell adhesion.

70. A method for identifying a cyclic peptide capable of modulating cadherin-mediated cell adhesion, comprising:

(a) contacting an epithelial surface of skin with a test marker in the presence and absence of candidate cyclic peptide; and

(b) comparing the amount of test marker that passes through said skin in the presence of candidate cyclic peptide to the amount that passes through skin in the absence of candidate cyclic peptide, and therefrom identifying a cyclic peptide capable of modulating cell adhesion.

71. A method according to claim 70, wherein said skin is human skin.

72. A method for identifying a cyclic peptide capable of modulating cadherin-mediated cell adhesion, comprising:

(a) contacting a blood vessel with a candidate cyclic peptide; and

(b) comparing the extent of angiogenesis of said blood vessel to a predetermined extent of angiogenesis observed for a blood vessel in the absence of candidate cyclic peptide, and therefrom identifying a cyclic peptide capable of modulating cell adhesion.

73. A kit for administering a drug via the skin of a mammal, comprising

(a) a skin patch; and

(b) a cyclic peptide according to any one of claims 1-19.

74. A kit according to claim 73, wherein said skin patch is impregnated with said cyclic peptide.

75. A kit according to claim 74, further comprising a drug.

76. A method for modulating cell adhesion, comprising contacting a cadherin-expressing cell with an antibody that binds to a cyclic peptide according to any one of claims 1-19.

77. A method for targeting a drug to a cadherin-expressing cell in a mammal, comprising administering to a mammal an antibody that binds to a cyclic peptide according to any one of claims 1-19, wherein said antibody is linked to a drug.

78. A method for detecting the presence of cadherin-expressing cells in a sample, comprising:

(a) contacting a sample with an antibody that binds to a cyclic peptide according to any one of claims 1-19 under conditions and for a time sufficient to allow formation of an antibody-cadherin complex; and

(b) detecting the level of antibody-cadherin complex, and therefrom detecting the presence of cadherin expressing cells in a sample.

79. A method according to claim 78, wherein said antibody is linked to a support material.

80. A method according to claim 79, wherein said antibody is linked to a detectable marker.

81. A method according to claim 80, wherein said detectable marker is a fluorescent marker, and wherein the step of detecting is performed using fluorescence activated cell sorting.

82. A kit for detecting the presence of cadherin-expressing cells in a sample, comprising:

(a) an antibody that binds to a cyclic peptide according to any one of claims 1-19; and

(b) a detection reagent.

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